Anesthesia enhances subthreshold critical slowing-down in a stochastic Hodgkin-Huxley neuron model

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Introduction

Critical slowing down—nonlinear growth in amplitude simultaneous with decay in frequency of soma voltage fluctuations—has been observed in neurons on close approach to spiking threshold [1]. This nonlinear dynamical phenomenon has been demonstrated to arise spontaneously in single neuron models with stochastic ion channel kinetics [2] as well as in mean-field theories of neural populations during the anesthetic-induced awake-to-unconscious phase transition [3]. However, theoretical and computational studies of the influence of anesthesia on the dynamics of single neurons are sparse and the biophysical mechanisms of anesthesia across the organizational levels of the central nervous system remain poorly understood. Because critical slowing down may prove to be a biophysically significant mechanism mediating neuron-to-neuron communication as well as a means for monitoring the anesthetic-induced phase transition, we seek to further understand the impact of anesthesia on the subthreshold dynamics of single neurons.

Point Neuron Model

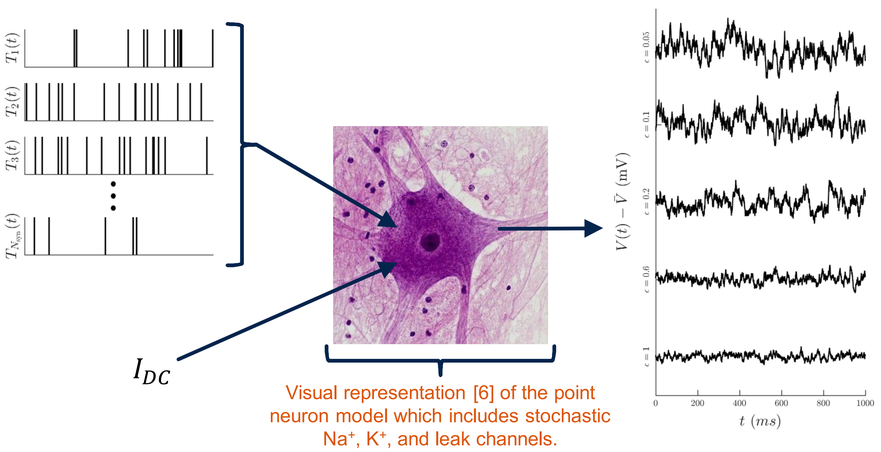
We investigated the influence of GABAergic anesthesia on the critically slowed subthreshold dynamics of a model Hodgkin-Huxley point neuron endowed with stochastic sodium and potassium channel dynamics and driven by multiple synapses designed to mimic phasic $GABA_A$ inhibition. The model is composed of the following set of stochastic differential equations

$$C\frac{dV}{dt} = I_{\mathrm{DC}} - \bar{g}_{\mathrm{Na}}\, X_{\mathrm{Na}}^{\mathrm{open}}(V - E_{\mathrm{Na}}) - \bar{g}_{\mathrm{K}}\, X_{\mathrm{K}}^{\mathrm{open}}(V - E_{\mathrm{K}}) - g_{\mathrm{L}}(V - E_{\mathrm{L}}) - \frac{\bar{g}_{\mathrm{GABA}}}{N_{\mathrm{syn}}}\sum_{i=1}^{N_{\mathrm{syn}}} r_i\,(V - E_{\mathrm{GABA}})$$

$$\frac{d\mathbf{X}_j}{dt} = \mathbf{A}_j\,\mathbf{X}_j + \frac{1}{\sqrt{N_j}}\,\mathbf{S}_j(\mathbf{X}_j)\,\boldsymbol{\xi}_j(t) \quad \text{for} \quad j \in \{\mathrm{Na}, \mathrm{K}\} \quad \text{and} \quad \boldsymbol{\xi}_j(t) \sim \boldsymbol{\mathcal{N}}(0,1)$$

$$\frac{dr_i}{dt} = \alpha\, T_i(t)\,(1 - r_i) - \frac{\beta}{\gamma}\, r_i \quad \text{for} \quad i \in \{1, 2, \ldots, N_{\mathrm{syn}}\}$$

where standard nomenclature applies [V is voltage; I_{DC} an injected stimulus current; $\boldsymbol{X}_{Na}$and $\boldsymbol{X}_K$ are vectors containing the fractions of Na^+ and K^+ channels in each state of their associated Markov chains; r_i describes the saturating activation of the i^{th} $GABA_A$ synapse with decay rate β, anesthetic effect parameter $\gamma \geq 1$, and driven by a Poisson distributed sequence of presynaptic impulses $T_i(t)$]. Parameterized as a type-I integrator consistent with pyramidal neuron behavior [4], the primary components of the model are illustrated below. Distance from spiking threshold is measured by the dimensionless quantity $\epsilon = (I_{DC}^{crit} - I_{DC})/I_{DC}^{crit}$, where I_{DC}^{crit} is the spiking threshold.



Visual representation [6] of the point neuron model which includes stochastic Na^+, K^+, and leak channels.

Numerical Results

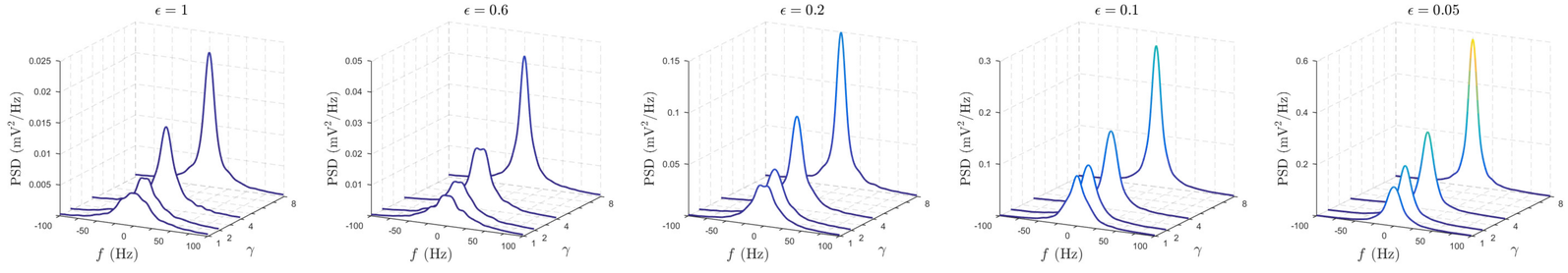


Fig 1 Voltage fluctuation power spectral densities (PSD) as the critical current for spike formation is approached from below for a selection of distances from threshold (ϵ, decreasing from left to right) and anesthetic effect parameter values (γ). Note divergence of the zero frequency magnitude with increasing γ (for set ϵ) and decreasing ϵ (for set γ).

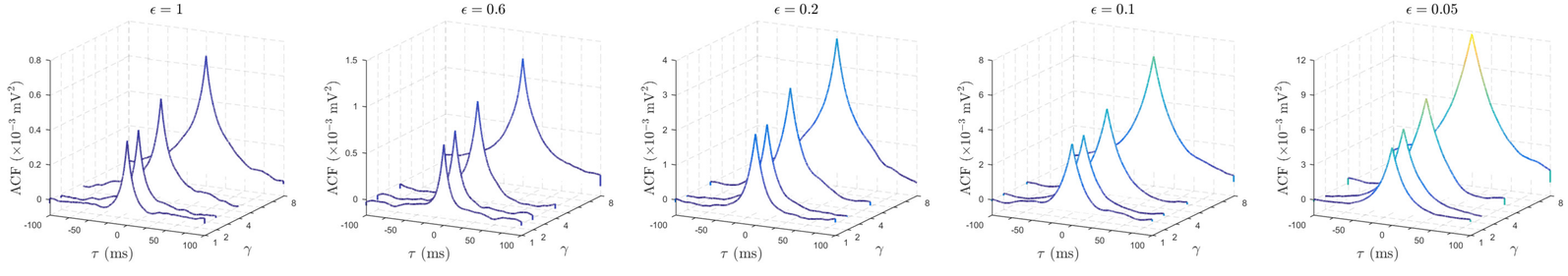


Fig 2 Voltage fluctuation autocorrelation functions (ACF) as the critical current is approached from below for a selection of distances from threshold (ϵ, decreasing from left to right) and anesthetic effect parameter values (γ). Note the surge in variance (zero-lag ACF magnitude) and increasing temporal persistence with increasing γ (for set ϵ) and decreasing ϵ (for set γ).

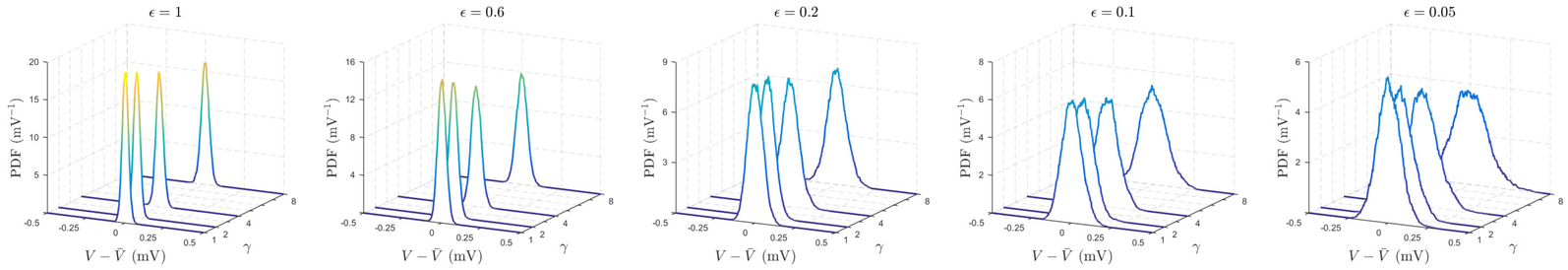


Fig 3 Voltage probability distribution densities (PDF) as the critical current is approached from below for a selection of distances from threshold (ϵ, decreasing from left to right) and anesthetic effect parameter values (γ). Note broadening of the distributions, corresponding to increased fluctuation amplitudes, with increasing γ (for set ϵ) and decreasing ϵ (for set γ).

Modeling Anesthesia

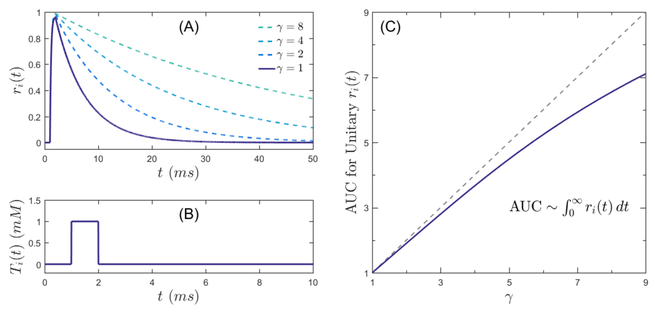


Fig 4 Anesthesia is modeled by reducing the unitary synaptic response decay rate β via the parameter $\gamma \geq 1$, where $\gamma = 1$ corresponds to the condition of no anesthesia (A). Presynaptic impulses [5] are modeled as 1 ms wide square waves of magnitude 1 mM (B). The integrated area under the curve (AUC) of the unitary synaptic response, normalized to the $\gamma = 1$ value, as a function of γ is shown in (C). Note the approximate linear relationship, consistent with experimental observations.

Discussion

- As anesthetic effect is increased, the statistical signatures of critical slowing-down are enhanced in magnitude.
- This finding is experimentally testable and supports the hypothesis that critical slowing-down is a conserved dynamical phenomenon across the organizational levels of the central nervous system during the awake-to-unconscious transition induced by anesthetics.
- Future work will include investigations for the presence of anticipated power-law scaling relationships and the inclusion of excitatory synaptic interactions to determine the robustness of these results.

References

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[6] Image obtained from www.quora.com/What-are-the-parts-of-the-neuron-and-their-function (accessed on 7/13/2017).

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